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Gender-related differences in clinical status in patients with persistent atrial fibrillation

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Abstract
Aim of the study was to evaluate gender-related differences in clinical status in patients with persistent non-valvular atrial fibrillation who were undergoing electrical cardioversion.
Materials and Methods: We have examined 141 patients with persistent NVAF who were undergoing electrical cardioversion. Patients were examined: general clinical methods, assessment of clinical symptoms and background heart disease, BMI calculation, measurement of blood pressure, determination of laboratory parameters. All patients underwent ECG and transthoracic echocardiography. Patients were divided into two subgroups depending on gender.
Results: Women with atrial fibrillation, which had sinus rhythm recovered by the electrical cardioversion, are older than men, they have a combination of several comorbid diseases and a higher risk of thromboembolic complications. Their clinical status is characterized by more symptomatic manifestations of arrhythmia, more severe HF and a significant renal impairment. Men are more prone to bad habits (smoking and alcohol abuse).

Keywords: atrial fibrillation, gender differences, electrical cardioversion

Introduction
Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia and a major risk factor for ischemic stroke and peripheral embolism. In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million [1]. AF in the general male population develops more often than in female, but after age 75 years, about 60% of the people with AF are women [2].
Recent studies demonstrated gender-related differences in clinical presentation, outcome, and management of patients with AF. This arrhythmia is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men [3]. Female AF patients who have additional stroke risk factors (particularly older age) are also at greater risk than men of having a stroke [4]. Women with diagnosed AF can be more symptomatic than men and are typically older with more comorbidities [5, 6] but women appear less likely to receive specialist care and rhythm control therapy [7] while the outcomes of catheter ablation or AF surgery are comparable to those in men [8].
The analysis of the data of the AF - CARAF, FRACTAL, AFNET registers has shown that women with AF are more likely to seek for medical help, notice more significant influence of arrhythmias at the quality of life and they have the paroxysms of AF more often than men do [9].
Women are significantly undertreated, have a worse outcome, and importantly a reduced efficacy of the rhythm control strategy that appears to enhance cardiovascular morbidity and mortality. Furthermore, a decreased quality of life (QoL) in women vs. men regardless of treatment strategy (rhythm vs. rate control) has been recognized [10].
These observations highlight the need to offer effective diagnostic tools and therapeutic management equally to women and men.
Aim of the study was of the study was to evaluate gender-related differences in clinical status in patients with persistent non-valvular atrial fibrillation (NVAF) who were undergoing electrical cardioversion (ECV).

Materials and Methods
We have examined 141 patients with persistent NVAF who were undergoing electrical cardioversion. The median of age (of lower-upper quartile) was 64 (57-70) years old. There were 95 (67%) men and 46 (33%) women in this study.
38 (27%) patients have had the atrial fibrillation detected for the first time. Median follow-up

of arrhythmia was 2.0 years (0.83-4.0): 24 (17.0%) patients have had the atrial fibrillation diagnosed more than five years ago, 21 (15%) - up to 5 years ago, there were 48 patients (34%) who have had it detected less than 1 year and 48 patients - up to 3 years ago. The median duration of the last episode of AF was 4 months (2.0-7.0).

AF was associated with arterial hypertension (AH) - 81.6% of patients, obesity (63.1%) and ischemic heart disease (IHD) - 26.2% of patients. Most often, patients had the combination of 2 main diseases (AH and obesity) - 36.9%, 17.7% of patients had the combination of 3 diseases (IHD, AH and obesity), 4 diseases (IHD, AH, obesity and chronic kidney disease) - 10.6%. Only 8 patients (5.7%) had neither concomitant cardial pathology nor overweight. The study excluded patients with valvular heart disease, cardiomyopathy, constrictive pericarditis, heart failure in NYHA functional class IV, stage 3 hypertension (systolic BP ≥180 or diastolic BP ≥110 mmHg), decompensated hypo- or hyperthyroidism, patients who have undergone ablation.

Patients were examined: general clinical methods (review of complaints, case history, life history), assessment of clinical symptoms and background heart disease, BMI calculation, measurement of blood pressure, determination of laboratory parameters. All patients underwent ECG and transthoracic echocardiography.

For statistical analysis of the results we used biometric analysis methodology supported by STATISTICA 6.1 software. Normal distribution was analysed by the mean value and mean error while non-normal distribution was analysed by the median and quartiles (Me [25–75]). Evaluation of the hypotheses was done using the Student's t-criterion for comparison of mean variables and indicators for relative share. Differences were considered significant at $p<0.05$.

Results and Discussion

The ratio of men and women among patients with persistent non-valvular AF is 2:1. The mean age of males is 60.6 ± 9.7 years old and women - 67.0 ± 8.2 years ($p<0.0001$). By the time of inclusion in the research females were significantly older: 63% of women were over 65 years old, while almost 70% of males were under 65 years old ($p<0.0001$). Among all patients there were 79.5% of males under 65 years old and 20.5%. of such women.

By the moment of the AF episode, which was detected for the first time, females were significantly older (on the average 7 years older - 64.0 ± 8.1 vs. 57.4 ± 10.4, $p<0.0001$).

It is important that the duration of the anamnesis of arrhythmia of examined males and females did not differ - 3.2 ± 3.3 years and 3.2 ± 3.6 years. It should be noted that the third part of men (32.6%) was with the episode of arrhythmia detected for the first time, what is, although, not veraciously, but more than among women (19.6%) (p = 0.1). Males had less median of duration of the last relapse of arrhythmia than females (5.1 ± 4.9 months vs. 6.8 ± 6.3, p = 0.1) (Table 1).

Table 1: Demographic features of the patients with persistent AF according to gender, M±SD (%)

	Men, n=95	**Women, n=46**	**p**
Ratios	2	1	
Age	60,6±9,7	67,0±8,2	$p<0,0001$
Under 65 years old	66 (69, 5%)	17 (37%)	$p<0,0001$
Over 65 years old	29 (30, 5%)	29 (63%)	$p<0,0001$
Since the beginning of arrhythmia, years old	57,4±10,3	64±8,1	$p<0,0001$
Under 65 years old	73 (76, 8%)	26 (56, 5%)	$p<0,05$
Over 65 years old	22 (23, 2%)	20 (43, 5%)	$p<0,05$
Duration of anamnesis of arrhythmia, years	3,2±3,3	3,2±3,6	0,999
AF diagnosed for the first time	21 (32, 6%)	9 (19, 6%)	p<0,1
Duration of the last relapse of AF, months	5,1±4,9	6,8±6,3	p<0,1
ECV in anamnesis			
1time	16 (16, 8%)	5 (10, 9%)	
>1 time	12 (8, 43%)	4 (12, 6%)	

Atrial fibrillation was symptomatic (EHRA> 1) for all the women without exception, while 25% of males did not feel any symptoms of arrhythmia ($p<0.00001$). Subjective symptoms of arrhythmia of more than half of the females (58.7%) were III functional class according to EHRA symptom scale, what is more than among males (45.3%; p = 0.1). (Figure 1). The most common symptoms of arrhythmia were feeling of intense heartbeat, heart failure, dyspnea and weakness.

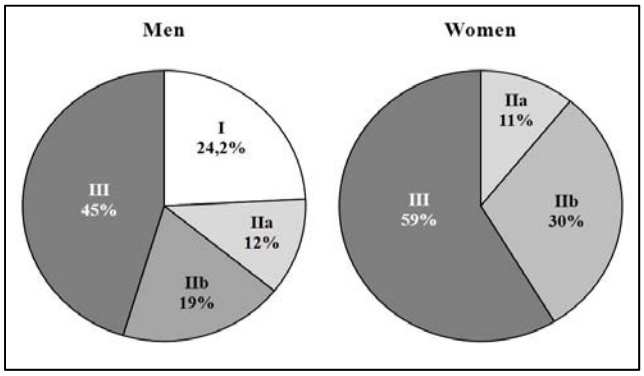

Fig 1: Symptom severity according to EHRA symptom scale in patients with persistent AF.

Among the risk factors for cardiovascular diseases, males often had harmful habits: smoking (41.1% vs. 6.5%; $p<0.0001$) and alcohol abuse (13% vs. 5%; $p<0.01$)
The risk of thromboembolic complications (TEC) according to the CHA2DS2-VASc among females on average was 4±1.7 points, and among males it was 2.2 ±1.6 points ($p<0.0001$). Males often had a low risk of TEC: 14, 7 % didn`t have any AF (0 points), 20% had 1 point, 32,6% ($p<0,05$) had 2 points. Females in contrast with males more often had TEC in anamnesis (24% vs. 16.8%; $p<0.05$). (Table 2).

Table 2: Risk factors for cardiovascular diseases and thromboembolic complications for patients with persistent AF according to gender, abs. (%)

	Men, n=95	**Women, n=46**	**p**
Family history of AF	22 (23%)	8 (17,4%)	$p<0,5$
Smoking	39 (41,1%)	3 (6,5%)	$p<0,0001$
Alcohol abuse	13 (13,7%)	2 (4,3%)	$p<0,05$
CHA2DS2-VASc score	2.2±1.6	4.0±1.7	$p<0,0001$
0 points	14 (14.7%)	0	$p<0,0001$
1 point	19 (20%)	4 (8.7%)	$p<0,05$
2 points	31 (32.6%)	4 (8.7%)	$p<0,0001$
3 points	11 (11.6%)	10 (21.7%)	$p<0,0001$
≥4 points	20 (21.1%)	28 (60.9%)	

The most common diseases associated with arrhythmia were combinations of arterial hypertension and obesity: almost half of the examined females (44%) and the third part of the males (34%) had it (Figure 2).
Despite the fact that both sexes have the same anamnesis of arrhythmia, AF of the majority of females (59%) has appeared for the first time on the background of prolonged arterial hypertension (about 10-15 years). 54% of males have had arterial hypertension and AF diagnosed at the same time ($p<0.01$). However, women with arterial hypertension controlled their pressure more carefully than men.
Atrial fibrillation of females more often developed depending on several background conditions. 15% of women have had the combination of 5 chronic diseases (IHD, AH, obesity, heart failure (HF), chronic kidney disease (CKD) diagnosed, this index for men was 5.3% ($p<0.05$). 28.3% of females vs. 11.6% of males ($p<0.05$) had the combination of 3 diseases (AH, obesity and CKD).
Man had lower symptoms of HF: 20% of patients had the first functional class HF according to the NYHA classification, and in the group of females only 8,7% ($p<0,05$) had it. Arrhythmia recurrence arose on the background of HF in 37% of women, which is more than in the group of men (23.2%, $p<0.05$).
Women were more likely to have moderate reduction in glomerular filtration rate (Stage IIIb) - 30.4% vs. 11.6% of men ($p<0.05$). The majority of males (59%) had a decrease of glomerular filtration rate of the second stage, the percentage of females was twice less (32%) ($p<0.01$).

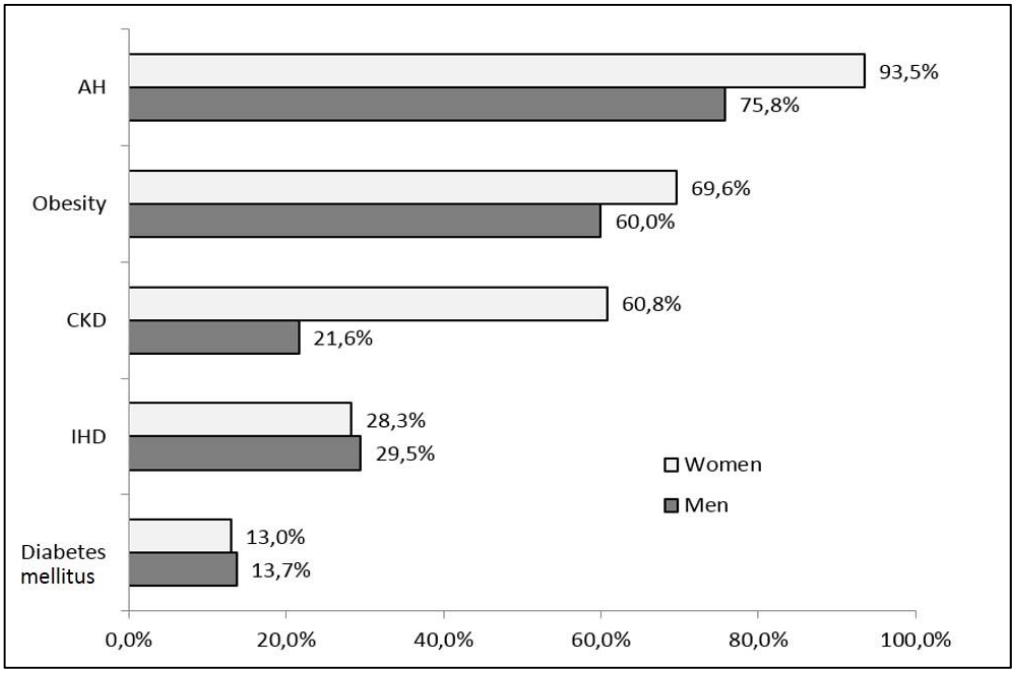

Fig 2: Cardiovascular diseases associated with persistent atrial fibrillation according to gender.

Conclusion
Women with atrial fibrillation, which had sinus rhythm recovered by the electrical cardioversion, are older than men, they have a combination of several comorbid diseases and a higher risk of thromboembolic complications. Their clinical status is characterized by more symptomatic manifestations of

arrhythmia, more severe HF and a significant renal impairment. Men are more prone to bad habits (smoking and alcohol abuse).

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